Systematic Review and Meta-Analysis

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Prognostic significance of matrix metalloproteinase 9 expression in osteosarcoma

A meta-analysis of 16 studies

Jian Zhou, MM[a,b], Tang Liu, MD[a], Wanchun Wang, MD[a,*]

Abstract

Background: Matrix metalloproteinase 9 (MMP-9) is significant in the progression of osteosarcoma (OS) via increasing tumor growth, invasion and metastasis. Although previous reports indicate the prognostic value of MMP-9 in OS, there is still a great degree on inconsistency between studies. Here we report a comprehensive evaluation of the value of MMP-9 in metastasis of OS by conducting a meta-analysis of published studies.

Methods: The quantity of the studies was evaluated using the Newcastle-Ottawa quality assessment scale (NOS). Sixteen studies with a total of 816 patients with OS were examined and we calculated the pooled odds ratio (OR) with corresponding 95% confidence interval (CI) (95% CI) to evaluate that the positive expression of MMP-9 predicts neoplasm metastasis and poor survival in OS.

Results: The results of Meta-analysis indicated that patients with positive expression of MMP-9 were significantly associated with neoplasm metastasis (OR = 4.69, 95% CI: 3.05–7.21, $P < .001$) and poor survival in OS with the pooled OR of 7.19 (95% CI 4.32–11.98, $P < .001$) when compared to their counterparts with a negative expression of MMP-9. The results of sensitivity analysis showed that the pooled OR was stable. It doesn't significantly change when a single study was removed.

Conclusions: The results of meta-analysis indicated that MMP-9 may be a prognostic biomarker guiding the clinical therapy for OS.

Abbreviations: CI = confidence interval, CNKI = China National Knowledge Internet, ECM = extracellular matrix, MMP-9 = matrix metalloproteinase 9, MMPs = matrix metalloproteinases, NOS = Newcastle-Ottawa quality assessment scale, OR = odds ratio, OS = osteosarcoma.

Keywords: meta-analysis., metastasis, MMP-9, osteosarcoma, overall survival

1. Introduction

Osteosarcoma (OS), the most common malignant bone tumor, is limited to the metaphysis of long bones and mainly afflicts adolescents.[1,2] Recently, the 5-year survival rate of OS patients has significantly improved to 70% due to the introduction of advanced surgery and combinational chemotherapy.[3] However, with the fact that most of OS patients are involved in fatal metastasis, which dramatically reduces survival rates, OS is still the second leading cause of cancer-related death in adolescents.[4,5] Previous studies showed that approximately 20% to 25% of newly diagnosed patients have detectable lung-related metastasis,[6,7] but at present, the ability to predict the metastasis of OS is limited because the mechanism of oncogenesis is still not fully elucidated and the clinical prognostic factors of OS are still demographics (such as age and sex), tumor size and response to chemotherapy. So to identify prognostic markers in OS may be an informative way for selecting proper management.

The function of zinc-dependent endopeptidases is to degrade the extracellular matrix (ECM). Matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases, participate in many pathological and physiological processes, such as tissue repair and remodeling.[8] Moreover, MMPs play a significant role in tumor progression via increasing cell growth, migration, invasion and metastasis.[7] Recently, considerable interest has been focused on an important MMP family member, matrix metalloproteinase 9 (MMP-9) because of its over-expression in various tumors and association with poor disease prognosis in gastric and oral cancers.[9,10] The potential prognostic value of MMP-9 in OS has also been examined. However, no conclusions have been reached due to inconsistent results between studies.[11–13] Like most sarcomas, blood-borne metastases often occur in OS. Metastatic lesions found in the lung, liver, brain, bone, kidney, and local lymph nodes were defined as metastasis.[14–18] In this study, a meta-analysis was conducted to provide a comprehensive evaluation of the relationship between positive expression of MMP-9 and OS metastasis.

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2. Materials and methods

2.1. Search strategy and study selection

A systematic search was conducted to search for relevant articles in PubMed, Embase, and China National Knowledge Internet (CNKI) databases. We performed the last search on March 20, 2018. The following terms: "OS" or "osteosarcomas" and "matrix metalloproteinase-9" or "MMP-9" were included in the search strategy without language limitation. Because this analysis was based on previously published studies, the ethics approval was not applicable.

2.2. Inclusion and exclusion criteria

Inclusion criteria:

(1) measurement of MMP-9 in OS using commercial reagents;
(2) pathological diagnosis (gold standard) confirmed for newly diagnosed patients with OS;
(3) the studies had to provide sufficient information to construct the 2×2 contingency table;
(4) publications were written in English or Chinese.

Exclusion criteria:

(1) OS diagnosed without a biopsy and there was no clear cut-off value in the literature;
(2) similar studies from the same author as well as multiple duplicate data in the different works, excluding earlier and smaller sample data;
(3) cell and animal experiments, reviews, correspondences, case reports, talks, letters, expert opinions, and editorials without original data; and
(4) studies of non-dichotomous MMP-9 expression levels and absence of survival outcome.

2.3. Data extraction

Two investigators (JZ and TL) evaluated the eligibility of all retrieved studies and extracted the relevant data independently. Extracted databases were then crosschecked between the 2 authors to rule out any discrepancy. Data regarding the following for each included studies were extracted independently: first authors' surname, publication year, MMP-9 assessment methods, and the cut-off definition. Corresponding authors were contacted if further information was needed. The study was excluded if no response was received after sending a reminder.

2.4. Assessment of included studies

The Newcastle-Ottawa quality assessment scale (NOS)[19] was used to assess the quality of included studies. It has 3 categories (selection, comparability, and exposure) and 8 items. The quality assessment values ranged from 0 to 9 stars. Studies that scored more than 6 stars were included for our analysis.

2.5. Statistical analysis

The pooled odds ratio (OR) with corresponding 95% confidence interval (CI) was calculated to evaluate the effect of MMP-9 positive expression on metastasis and poor survival of OS. The heterogeneity between the included studies was assessed by I^2 statistics, which quantified the proportion of the total variation in meta-analysis assessment from 0% to 100%.[20] When there was no significant heterogeneity ($I^2 \leq 50\%$), the fixed effects model was used[21]; otherwise, a random effects model was used for the analysis.[22] Moreover, sensitivity analysis was performed by sequentially omitting individual studies to assess the stability of the results. The possibility of publication bias was assessed via visual assessment of the symmetry of Egger test and Begg funnel plots.[23] All the analyses were performed by using STATA version 12 software (StataCorp LP, College Station, TX). A 2-tailed $P < .05$ was considered statistically significant.

3. Results

3.1. Selection and characteristics of included studies

Through the primary search in PubMed, Embase, and CNKI databases and further evaluation of full texts, 16 studies[12,13,24–37] with a total of 816 patients with OS were included in the meta-analysis (Fig. 1). Among the 16 studies, 12 were published in Chinese and the other 4 were published in English. There are 3 studies[25,29,32] included in both OS metastasis meta-analysis and overall survival meta-analysis. The sample size of the 11 studies for OS metastasis ranged from 35 to 96 with a mean of 65.5 (Table 1) and the sample size of the 8 studies for OS overall survival ranged from 21 to 96 with a mean of 58.5 (Table 2). The main characteristics of the included studies were summarized in Tables 1 and 2. In summary, immunohistochemistry (IHC) was used for all studies to detect the expression of MMP-9. The results were judged via cut-off in percentage of positivity.

3.2. Qualitative assessment

The study quality was assessed using the NOS, generating scores ranging from 7 to 8 (with a mean of 7.42). A higher value (0–9) indicates better methodology. The results of the quality assessment are shown in Tables 1 and 2, with detailed information shown in Supplementary Table 1, http://links.lww.com/MD/C599 and Supplementary Table 2, http://links.lww.com/MD/C599.

3.3. Meta-analysis

In the meta-analysis assessment of the effect of MMP-9 positive expression on OS metastasis and overall survival, STATA 12 indicated there was no significant between-study heterogeneity among those studies analyzed for the metastasis or overall survival of MMP-9 ($I^2 < 35\%$), so the fixed-effect model was used to detect the pooled OR with corresponding 95% CI. The combined OR for all eligible studies evaluating MMP-9 positive expression on metastasis and poor survival in OS was (OR = 4.69, 95% CI: 3.05–7.21, $P < .001$) and (OR = 7.19, 95% CI 4.32–11.98, $P < .001$) respectively (Fig. 2).

The expression cutoff value of MMP-9 is different among these studies. In order to eliminate the bias caused by different MMP-9 expression cut-off value, we performed a subgroup analysis to eliminate the bias caused by different MMP-9 expression cutoff value. We found significant association in both studies with cut-off value of MMP-9 >20% (OR = 5.62, 95% CI = 3.27–9.66, P <.001) and studies with cutoff value of MMP-9 <20% (OR = 3.55, 95% CI = 1.76–7.14, $P < .001$) for MMP-9 positive expression on metastasis, as shown in Figure 2. No heterogeneity was found between these 2 groups.

Moreover, for MMP-9 positive expression on overall survival, significant association in both studies with cut-off value of MMP-9 >20% (OR = 4.34, 95% CI = 2.08–9.07, $P < .001$) and studies with cut-off value of MMP-9 <20% (OR = 11.71, 95% CI =

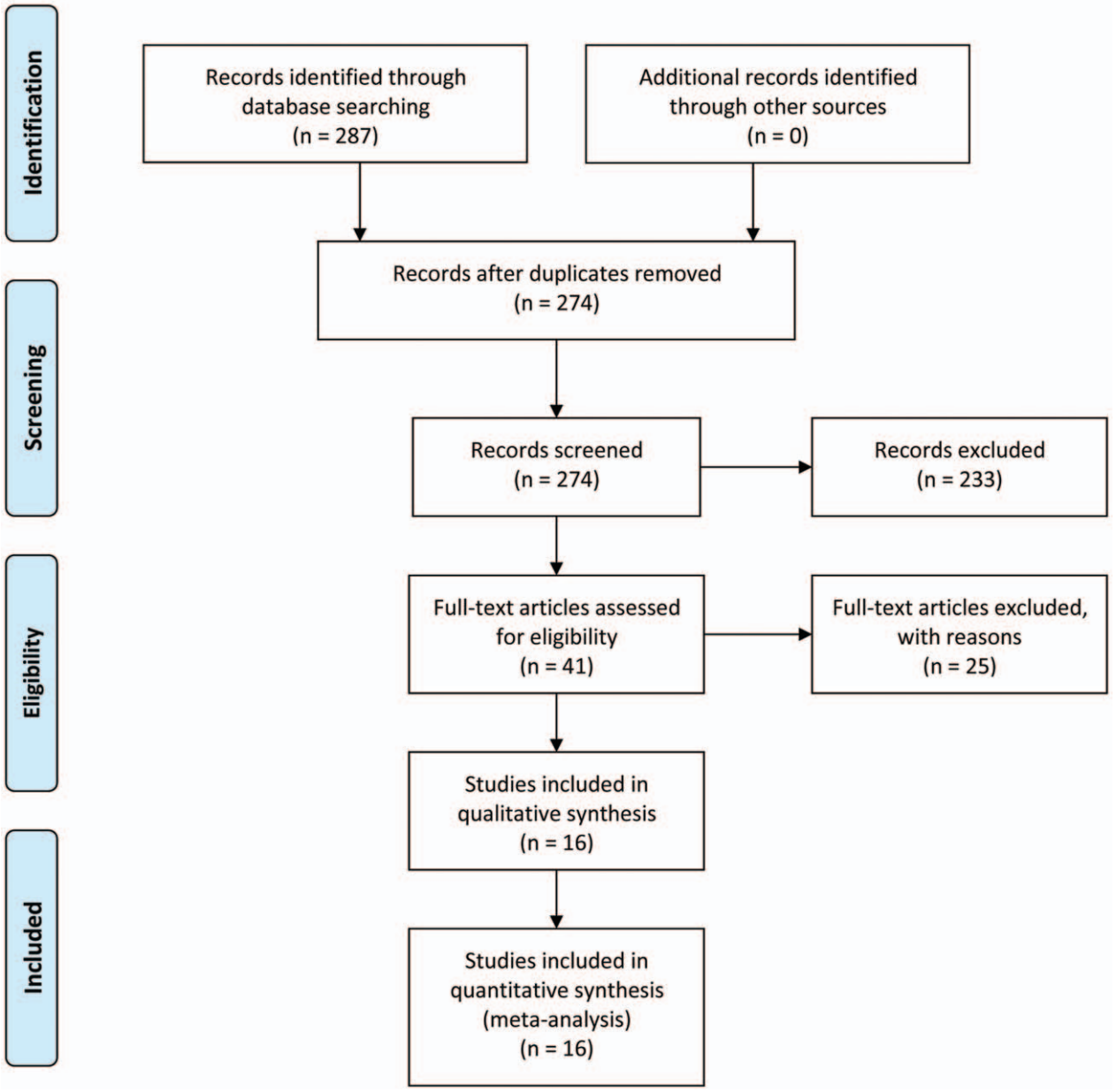

Figure 1. Schematic representation of the study selection.

Table 1

Characteristics of studies included in the metastasis meta-analysis.

REF	Study	Year	No. of patients	Age (median)	Method	Assay kit	MMP-9 cut-off	MMP-9 positive		MMP-9 negative		NOS score
								Metastasis	Non metastasis	Metastasis	Non metastasis	
[25]	Wang et al	2017	71	18	IHC	ZSGB-BIO	>25%	40	13	3	15	7
[26]	Ren et al	2015	96	20	IHC	Abcam	≥20%	25	20	9	42	8
[27]	Lian et al	2013	35	21.1	IHC	–	>30%	20	5	4	6	8
[28]	Du et al	2010	41	20.38	IHC	ZSGB-BIO	≥10%	17	19	0	5	7
[29]	Li et al	2010	50	26.8	IHC	–	>5%	29	7	5	9	7
[30]	Huang et al	2009	61	28	IHC	Santa Cruz	>10%	37	12	5	7	8
[31]	Lv et al	2007	42	<15	IHC	Putin Kang	>25%	16	5	6	15	7
[32]	Liu et al	2007	45	22.5	IHC	MXB biotechnologles	>10%	8	32	1	4	7
[33]	Li et al	2006	56	18	IHC	OriGene	≥10%	5	25	3	23	8
[34]	Ferrari et al	2004	42	16	IHC	NeoMarkers	>20%	16	8	10	8	7
[35]	Peng et al	2002	62	17	IHC	MXB biotechnologles	≥5%	8	39	1	14	8

Table 2

Characteristics of studies included in the 3-year survival meta-analysis.

REF	Study	Year	No. of patients	Age (median)	Method	Assay kit	MMP-9 cut-off	MMP-9 positive		MMP-9 negative		NOS score
								Death	≥3-year survival	Death	≥3-year survival	
[26]	Ren et al	2015	96	20	IHC	Abcam	≥20%	16	29	9	42	8
[36]	Kushlinsky et al	2010	21	36.5	EIA	R&D	≥10%	5	8	0	8	7
[30]	Huang et al	2009	61	28	IHC	Santa Cruz	>10%	46	4	3	8	8
[37]	Luo et al	2006	33	16.7	IHC	MXB biotechnologles	≥20%	24	5	1	3	7
[33]	Li et al	2006	56	18	IHC	OriGene	≥10%	22	8	8	18	8
[38]	Li et al	2004	40	19.43	IHC	MXB biotechnologles	>10%	24	3	3	10	7
[39]	Foukas et al	2002	51	18	IHC	Binding Site Ltd	>10%	27	10	3	11	7
[40]	Chen et al	2001	70	22.04	IHC	–	>25%	51	10	3	6	8

5.72–23.98, $P<.001$) (Fig. 2). https://www.baidu.com/javascript: No heterogeneity was found between these 2 groups.

3.4. Sensitivity analysis

We used sensitivity analysis to evaluate the stability of results. As shown in Figure 3, all the heterogeneity did not change significantly no matter which study removed, which suggested that the results of our analysis did not overly rely on a single study and the conclusions are stable. All these results indicated that MMP-9 positive expression was an indicator of metastasis and overall survival for OS patients (Fig. 3).

3.5. Publication bias

Begg funnel plot and Egger test were performed to assess the publication bias in the meta-analysis. As shown in Figure 4, the funnel plot presented no obvious evidence of asymmetry among the 16 studies. Moreover, Egger test also revealed no significant publication bias in the meta-analysis ($P>.05$).

4. Discussion

OS is a primary life-threatening malignant bone tumor that often occurs in adolescents and young adults.[38] Disease 5-year survival rate escalated from <20% before the introduction of effective chemotherapy to around 60%.[39,40] With 20% to 25% detected metastases at diagnosis, OS is characterized by a high propensity for metastasis, especially to the lungs.[41] When metastasis is detected at the time of diagnosis, the overall survival rate of OS patients decreases to 30%. Early identification of high-risk patients may improve treatment by allowing clinicians to select the most appropriate therapy. Therefore, it is urgently needed to renew early prognostic biomarkers to adapt the proper therapy for the malignancy.

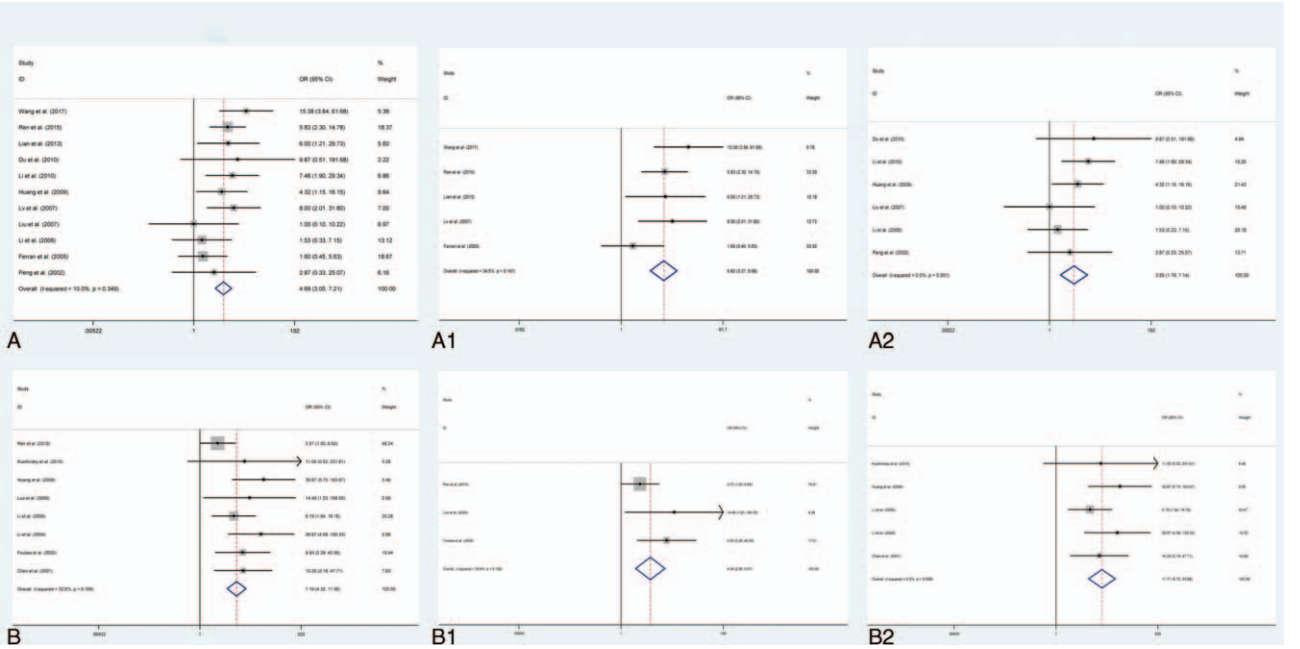

Figure 2. A. MMP-9 expression and metastasis of osteosarcoma patients. A1. MMP-9 expression and metastasis of osteosarcoma patients with cutoff value of MMP-9 >20%. A2. MMP-9 expression and metastasis of osteosarcoma patients with cutoff value of MMP-9 <20%. B. MMP-9 expression and overall survival of osteosarcoma patients. B1. MMP-9 expression and overall survival of osteosarcoma patients with cutoff value of MMP-9 >20%. B2. MMP-9 expression and overall survival of osteosarcoma patients with cutoff value of MMP-9 <20%.

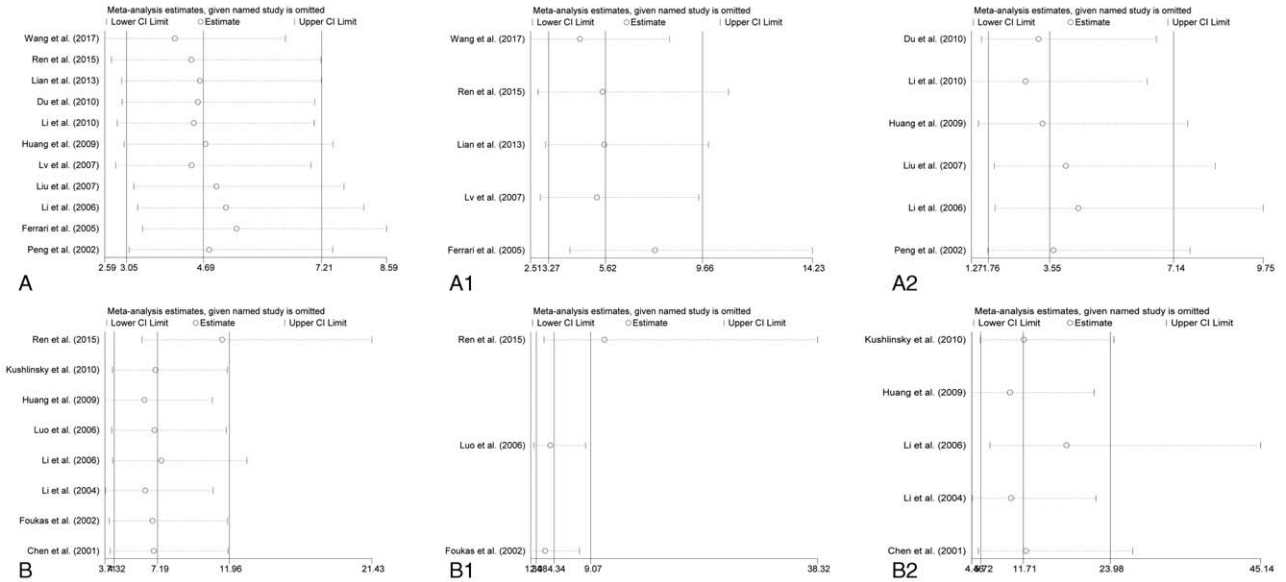

Figure 3. Forest plot for the sensitivity analysis in the meta-analysis. A. Metastasis. A1. Metastasis with cutoff value of MMP-9 >20%. A2. Metastasis with cutoff value of MMP-9 <20%. B. Overall survival. B1. Overall survival with cutoff value of MMP-9 >20%. B2. Overall survival with cutoff value of MMP-9 >20%.

MMPs play critical roles in tumor cell growth, migration, invasion, metastasis, and angiogenesis.[23,42] MMP-9, a member of MMPs family, mainly functions as a collagenase by degrading type IV collagen which is a major component of basement membrane and ECM.[43,44] According to the results of previous meta-analysis, there is an important correlation between high MMP-9 expression and poor prognosis in breast cancer,[45] gastric cancer,[46] colorectal cancer[47] and non-small cell lung cancer.[48] In this report, a similar approach was used to evaluate the prognostic value of MMP-9 positive expression in OS.

Meta-analysis is a quantitative approach combining information from different studies on the same topic, which has been used to evaluate prognostic markers for several cancers.[49] In order to conduct a precise assessment about the prognostic role of MMP-9 positive expression in OS, a meta-analysis was performed and 16 published studies were included. Our results indicated that MMP-9 positive expression in OS predicted a statistically significant role of MMP-9 on OS metastasis (OR = 4.69, 95% CI: 3.05–7.21, $P < .001$) and poor survival (OR = 7.19, 95% CI 4.32–11.98, $P < .001$) in OS (Fig. 2). Considering the expression cutoff value of MMP-9 is different among these studies, we conducted a subgroup analysis to rule out the potential bias caused by different MMP-9 expression cutoff values. We found significant association in both studies with cutoff value of MMP-

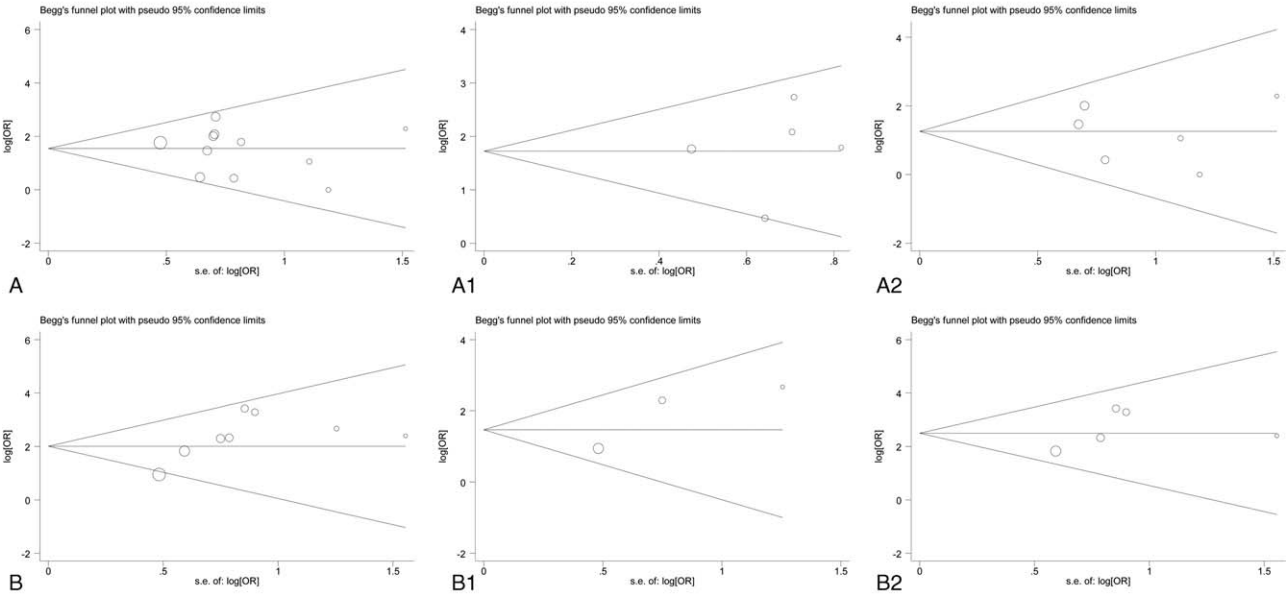

Figure 4. Funnel plot in the meta-analysis of the effect of MMP-9 expression on metastasis and overall survival of OS. A. Metastasis. A1. Metastasis with cutoff value of MMP-9 >20%. A2. Metastasis with cutoff value of MMP-9 <20%. B. Overall survival. B1. Overall survival with cutoff value of MMP-9 >20%. B2. Overall survival with cutoff value of MMP-9 >20%.

9 >20% (OR = 5.62, 95% CI = 3.27–9.66, $P < .001$) and studies with cutoff value of MMP-9 <20% (OR = 3.55, 95% CI = 1.76–7.14, $P < .001$) for MMP-9 positive expression on metastasis (Fig. 2). Additionally, for MMP-9 positive expression on overall survival, significant association in both studies with cutoff value of MMP-9 >20% (OR = 4.34, 95% CI = 2.08–9.07, $P < .001$) and studies with cutoff value of MMP-9 <20% (OR = 11.71, 95% CI = 5.72–23.98, $P < .001$) (Fig. 2). https://www.baidu.com/javascript: No heterogeneity was found between metastasis groups or survival groups. All these results indicated different expression cutoff values of MMP-9 did not affect the results significantly.

Then we conducted a sensitivity analysis to evaluate the stability of results, suggesting the pooled OR was stable and not significantly changed no matter which study removed (Fig. 3). A Begg funnel plot with STATA was performed and no publication bias was found ($P > .05$) (Fig. 4). This meta-analysis suggests that MMP-9 positive expression is associated with OS metastasis and overall survival. MMP-9 may be used as a prognostic biomarker to guide the clinical therapy for OS.

However, our meta-analysis has its limitations. There are several issues that should be considered.

The sample size of the total patients included in this meta-analysis was relatively small with a mean of 51. Additionally, there were 573 OS patients with MMP-9 positive expression and only 243 patients with MMP-9 negative expression. Random errors and sample bias are unavoidably produced due to the relatively small size.

In this meta-analysis, only articles published in English or Chinese were included, which may cause additional bias.

There was not any unified cut-off value for defining MMP-9 positive expression. Although we conducted a subgroup analysis to eliminate the potential bias, a standard threshold would be beneficial to make precise evaluation about the prognostic role of MMP-9 positive expression.

There is no publication bias. However, potential publication bias may still exist. These studies with desirable results may be published more easily, which may cause an over-estimation of overall accuracy.

We cannot stratify patient data by age, tumor stage, tumor size, and histological types due to lack of sufficient data. In order to strengthen our findings, well-designed clinical studies with larger sample size are needed to be performed in the future before the application of MMP-9 on the metastasis of OS patients. Although the inherent limitations of this meta-analysis are still exist, this meta-analysis presents a quantified synthesis of published studies, which may draw more attention on new prognostic biomarkers of OS.

In conclusion, a meta-analysis was conducted to evaluate the association between MMP-9 positive expression and prognosis, included metastasis and overall survival, of patients with OS. According to the results from the meta-analysis, MMP-9 is an effective biomarker that correlates with OS metastasis and poor survival. In order to obtain a more comprehensive evaluation about the prognostic role of MMP-9 positive expression in OS patients, more well-designed studies with larger sample sizes are still needed.

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Author contributions

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Formal analysis: Tang Liu, wanchun wang.
Funding acquisition: Jian Zhou, wanchun wang.
Investigation: Jian Zhou, wanchun wang.
Methodology: Jian Zhou.
Writing – original draft: Jian Zhou, wanchun wang.
Writing – review & editing: Jian Zhou, wanchun wang.

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